

# Hormone therapy for endometriosis and surgical menopause (Review)

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[Intervention Review]

# Hormone therapy for endometriosis and surgical menopause

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## ABSTRACT

### Background

Endometriosis is characterized by the presence of ectopic endometrial tissue that might lead to many distressing and debilitating symptoms. Despite available studies supporting standard hormone therapy for women with endometriosis and post-surgical menopause, there is still a concern that estrogens may induce a recurrence of the disease and its symptoms.

### Objectives

This review aimed to look at pain and disease recurrence in women with endometriosis who used hormone therapy for post-surgical menopause.

### Search strategy

We searched the Cochrane Menstrual Disorders and Subfertility Group Specialized Register (March 2008), Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 3), MEDLINE (1966 to March 2008), EMBASE (1980 to March 2008), and references lists of articles. Relevant journals and conference proceedings were handsearched.

### Selection criteria

Randomized controlled trials studying hormone therapy for women with endometriosis in post-surgical menopause.

### Data collection and analysis

Review authors assessed the eligibility of trials and their quality.

### Main results

Two studies fulfilled our inclusion criteria. One trial compared the nonstop transdermal application of 17 $\beta$ -estradiol (0.05 mg/day) combined with cyclic medroxy progesterone acetate (10 mg per day) for 12 days per month in women with a conserved uterus with nonstop tibolone (2.5 mg/day). The second trial used sequential administration of estrogens and progesterone with two 22 cm<sup>2</sup> patches applied weekly to produce a controlled release of 0.05 mg/day. Micronized progesterone was administered orally (200 mg/day) for 14 days with a 16-day interval free of treatment.

Pain and dyspareunia

The first trial reported recurrence of pain in the estrogen and progesterone arm in 4/10 of women compared with 1/11 in the tibolone arm. In the latter, 4/115 women reported recurrence of pain in the treatment group compared with 0/57 patients in the no-treatment arm. Neither finding was statistically different.

Confirmed recurrence or exacerbation of endometriosis

This outcome was not reported in the first trial. The second found that 2/115 of the treatment group developed recurrence of endometriosis with no recurrence reported in the no-treatment group. This was not statistically significant. No woman was re-operated on in the no-treatment group compared with 2/115 in the treatment group.

#### **Authors' conclusions**

Hormone replacement therapy for women with endometriosis in post-surgical menopause could result in pain and disease recurrence. However, the evidence in the literature is not strong enough to suggest depriving severely symptomatic patients from this treatment. There is a need for more randomised controlled studies.

## **PLAIN LANGUAGE SUMMARY**

### **Hormone therapy for women with endometriosis and surgical menopause**

Endometriosis is known to result in variable severity of symptoms. For some women bilateral removal of the ovaries (oophorectomy) with or without a hysterectomy may be required to manage symptoms. This brings women into premature menopause. It is thought that hormone replacement therapy may enhance the recurrence of the disease due to its effect on the remaining endometriotic deposits in the pelvis. Only two small randomised controlled were identified in the literature that looked at this problem. Further research is required to clarify the effect of different hormone replacement therapy types on the recurrence of the disease and the associated pain including during sex.

## BACKGROUND

Endometriosis is characterized by the presence of ectopic endometrial tissue that can lead to distressing and debilitating symptoms. The prevalence of endometriosis in the general population is not known but it has been estimated to affect about 7% of women of reproductive age (Haney 1991). Estimates of prevalence based upon visualization of the pelvic organs range from 1% to 50% (Chatman 1982; Sangi-Hagheykar 1995).

There is considerable controversy regarding the optimal treatment of endometriosis. The choice of therapy usually depends upon the severity of symptoms, extent and location of the disease, desire for pregnancy, and a woman's age (Shaw 1992).

Endometriosis is generally believed to be an estrogen-dependent disorder. The many observations that support this view include amelioration of pre-existing endometriosis after surgical menopause (Kitawaki 2002) or natural menopause (Kitawaki 2002), and the growth of endometrial tissue in animals on estrogen therapy (Bruner-Tran 2002). This has led to the use of gonadotropin-releasing hormone agonists (GnRHa) to induce ovarian suppression, which is widely accepted as a treatment for endometriosis. The fall in estrogen levels following treatment with GnRHa leads to a significant improvement in the stage and symptoms of endometriosis (Donnez 1997; Fedele 2004). This may be used as a short-term strategy due to the risk of developing osteoporosis (Agarwal 2002).

Inducing menopause, either medically or surgically, has become one of the strategies for the management of the symptoms of endometriosis. Hysterectomy is commonly performed for endometriosis. Generally the ovaries are conserved in order to avoid the need for lengthy hormone replacement therapy. Removal of both ovaries is usually considered appropriate when the woman is approaching menopause or in the presence of extensive disease. Sometimes hysterectomy and bilateral salpingoophorectomy are inadequate if deep disease is left untreated (Donnez 1997; Fedele 2004; Matorras 2002).

Surgical and medical menopause are frequently associated with hypo-estrogenic side effects and changes in bone density, although these may resolve with treatment (Slenvenson 1989). A number of studies have been conducted which investigated the effects of GnRHa ovarian suppression and progress of endometriosis (Cedars 1990; Makarainen 1996; Riis 1990; Surrey 1990). Others have investigated the effect of an add-back regimen that uses either estrogen or progestogens to avoid hot flushes (Cedars 1990; Riis 1990; Surrey 1992). Tibolone has also been evaluated, and shown to be effective, in a single small trial (Tabkin 1997). The results of this study showed that tibolone suppressed painful symptoms, vasomotor symptoms, and urinary markers of bone turnover.

Despite available evidence supporting standard hormone therapy for women with endometriosis post-surgical menopause (Lindsay

1996; Rock 1992), many gynaecologists remain concerned that estrogens may induce a recurrence of the disease and its symptoms. Several studies (Sagsaveen 2003) have been carried out to assess the effect of hormone therapy on hypo-estrogenic symptoms induced by GnRH analogues for women with endometriosis but only a few have addressed its effect on women experiencing post-surgical menopause.

The aim of this systematic review of published literature is to critically appraise the literature describing the risk of pain and disease recurrence among women who have had endometriosis and undergone bilateral salpingoophorectomy (BSO), with or without hysterectomy, and subsequently received hormone therapy.

## OBJECTIVES

This review aimed to look at pain recurrence for women with endometriosis who used hormone therapy for post-surgical menopause.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All randomised controlled trials (RCTs) which studied women with endometriosis taking estrogen replacement therapy (ERT) or hormone replacement therapy (HRT) following surgical menopause.

Non-randomized and quasi-randomized controlled trials were excluded.

#### Types of participants

##### Inclusion criteria

Women with ectopic endometrial tissue that potentially could lead to distressing and debilitating symptoms regardless of the size and site of the deposits. Women who had undergone bilateral oophorectomy for treatment of endometriosis. Surgical menopause was defined as menopause due to surgical excision of both ovaries, with or without hysterectomy.

##### Exclusion criteria

Studies with participants who didn't fulfil the inclusion criteria were excluded.

#### Types of interventions

1. Estrogen versus placebo
2. Estrogen versus progestogen
3. Estrogen versus tibolone
4. Estrogen versus estrogen plus progestogen
5. Estrogen versus other hormones

We included all dosages, routes of administration, and frequency or duration of intervention.

## Types of outcome measures

### Primary outcome measures

- Pain and dyspareunia (painful intercourse)

The method of pain assessment was identified and, if possible, the participants were grouped into three major groups of: mild, moderate, or severe pain.

### Secondary outcomes measures

- Confirmed recurrence or exacerbation of endometriosis (recurrence of disease symptoms that were suspected clinically and confirmed by tissue biopsy or ultrasound findings).
- Diagnosis of cancer (defined as the development of adenocarcinoma at the site of the endometriotic deposits).
- Mortality (death related directly or indirectly to the disease, its treatment, or both).
- Re-operation for endometriosis.

## Search methods for identification of studies

We obtained relevant trials from the following sources (with the most recent search done on 18th March 2008).

- 1) We searched the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL) (March 2008).
- 2) We searched MEDLINE using the optimally sensitive strategy for the identification of RCTs developed for The Cochrane Collaboration and a specific search strategy developed with input from the MDSG Trial Search Co-ordinators ([Appendix 1](#)).
- 3) We searched EMBASE using a search strategy adapted from that developed for The Cochrane Collaboration for the identification of RCTs and combined this with a specific search strategy developed with input from the MDSG Trial Search Co-ordinators ([Appendix 5](#)).
- 4) We searched CINHALL (1982 to 18 March 2008) ([Appendix 3](#)).
- 5) We searched PSYCINFO (1982 to 18th March 2008) ([Appendix 2](#)).
- 6) We also searched reference lists of standard Obstetrics and Gynaecology textbooks, review articles, and relevant trials.
- 7) We sent letters seeking information about unpublished or incomplete, ongoing trials to investigators known to be involved in previous trials.

## Data collection and analysis

### Selection of the studies

Four review authors (HK, AH, SH, HF) undertook study selection. We used the search strategy described above to obtain titles and abstracts of studies that may be relevant to the review. HK and AH independently screened the titles and abstracts of promising

articles. They discarded studies that were not applicable and retained studies and reviews that might have included relevant data or information. HK and AH independently assessed retrieved abstracts and ordered the full texts of these studies when necessary. We did not require translation of any studies reported in non-English language journals. Where more than one publication of a trial existed, we included only the publication with the most complete data. We resolved any disagreements through discussion. No crossover trials were included.

SH and HF independently assessed the quality of studies to be included, without blinding to authorship or journal of publication, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The review authors resolved discrepancies by discussion with HK and AH (see Table 1).

### 1. Selection bias (randomization and allocation concealment)

We assigned a quality score for each trial using the following criteria.

- A. Adequate concealment of allocation: telephone randomization, consecutively numbered sealed opaque envelopes.
- B. Unclear whether adequate concealment of allocation: list or table used, sealed envelopes, study did not report on any concealment approach.
- C. Inadequate concealment of allocation: open list of random number tables, use of case record numbers, dates of birth, or days of the week.

### 2. Performance bias (blinding of participants, researchers and outcome assessors)

We assessed blinding using the following criteria:

- A. blinding of participants (yes, no, or unclear);
- B. blinding of caregiver (yes, no, or unclear);
- C. blinding of outcome assessment (yes, no, or unclear).

### 3. Attrition bias (loss of participants, for example through withdrawals, dropouts, protocol deviations)

We assessed completeness of follow up using the following criteria:

- A. less than 5% loss of participants;
- B. 5% to 10% loss of participants;
- C. more than 10% and less than 20% loss of participants;
- D. more than 20% loss of participants.

We excluded all studies with more than 20% loss to follow up.

## Analysis

For dichotomous outcomes (mortality, recurrence, cancer diagnosis, pain, dyspareunia, and re-operation) we expressed results as odds ratios (OR) with 95% confidence intervals (CI). No continuous data were reported hence weighted mean differences were not used.

We analysed data on an intention-to-treat basis. We included in the analysis all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention.

### Heterogeneity

Heterogeneity was not tested as the two identified studies used different interventions.

### Subgroup analysis

No subgroup analysis was possible from this data.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

HK and AH carried out data extraction independently using standard data extraction forms.

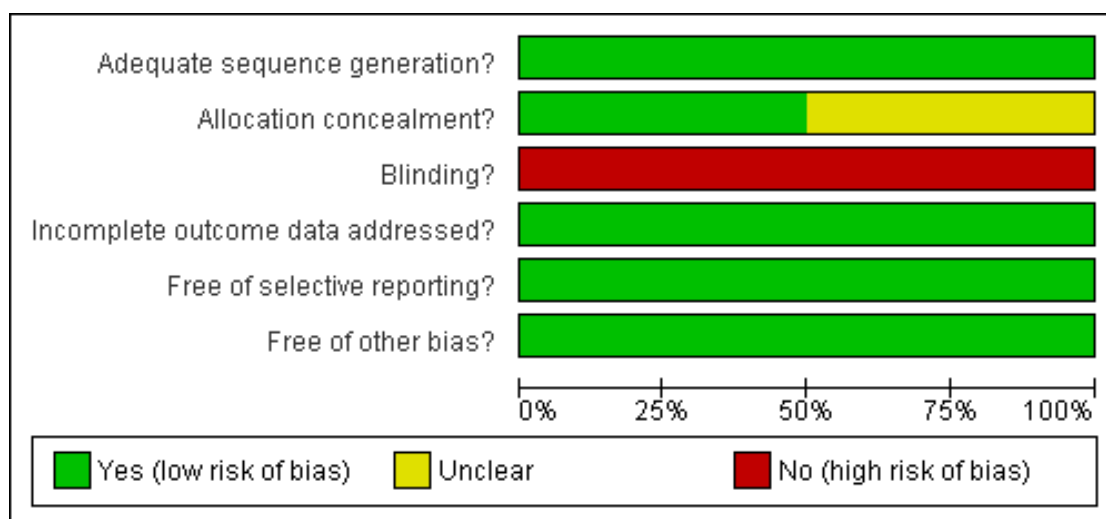
We intended to extract the following information from the two studies included in the review:

1. randomisation;
2. allocation concealment;
3. trial design multicentre or single centre, single phase or crossover;
4. number of patients randomised, excluded, and analysed;
5. duration, timing, and location of the trial;
6. source of funding;
7. type of surgical menopause;
8. type of intervention and control;
9. dose regime;
10. outcomes reported;
11. how outcomes were defined?
12. how outcomes were measured?
13. timing of outcome measurement.

### Risk of bias in included studies

The quality of the two included studies ([Fedele1999](#); [Matorras2002](#)) was adequate with a median Jadad score of 4 [Figure 1](#). [Figure 2](#)

**Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.**





**Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.**

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Fedele1999						
Matorras2002						

Fedele et al (Fedele1999) used computer-generated randomization while for Matorras et al (Matorras2002) randomization was by means of sealed envelopes with allocation done by a person not connected to the study. Allocation concealment was unclear for Fedele et al (Fedele1999). In Fedele et al (Fedele1999) there was no blinding as the two interventions were different while for Matorras (Matorras2002) the gynaecologist performing the follow up was kept blinded to the method of intervention. In both studies there were no dropouts and all patients were accounted for. Neither of the two studies declared the funding or sponsorship source nor any conflict of interest.

Statistical analysis was performed in accordance with the guidelines for statistical analysis developed by the Menstrual Disorders and Subfertility Group. Both trials were initially included in one analysis of hormone therapy for post-surgical menopause. Subgroup analysis was not possible as only two papers met the inclusion criteria. Results for each study were expressed as ORs with 95% CIs. Combined meta-analysis with RevMan software was not possible as the two studies used different interventions and controls, nor was statistical heterogeneity testing for the results of the two studies.

## Effects of interventions

Two studies fulfilled our inclusion criteria for hormone replacement therapy in patients with endometriosis and post-surgical menopause (Fedele1999; Matorras2002). Fedele et al (Fedele1999) compared nonstop transdermal application of 17 $\beta$ -estradiol 0.05 mg/day combined with cyclic medroxy progesterone acetate 10 mg/day for 12 days/month with nonstop tibolone 2.5 mg/day in women with a conserved uterus. Matorras et al (Matorras2002) used sequential administration of estrogen and progesterone following Belchetz's criteria (Belchetz 1994). Two 22 cm<sup>2</sup> patches were applied each week to produce a controlled release of 0.05 mg/day. Micronized progesterone was administered orally at a dose of 200 mg/day for 14 days with a 16-day interval free of treatment. This intervention arm was compared to the control group which did not receive treatment.

In Matorras et al (Matorras2002) the mean follow-up time was 45 months while Fedele et al (Fedele1999) followed up their participants for only 12 months. The main outcome studied by Matorras et al 2002 was recurrence of endometriosis diagnosed based on histological study, clinical findings, and ultrasound findings suggestive of endometriosis. Fedele et al (Fedele1999) used pain as the main outcome as reported by the participants at 3, 6, and 12-month follow-up visits after the start of the treatment.

### Pain and dyspareunia

In Fedele et al (Fedele1999) the number of women who reported

recurrence of pain in the estrogen and progesterone arm was 4/10 compared with 1/11 in the tibolone arm. There was no significant difference between the two groups (OR 6.67, 95% CI 0.60 to 74.51). The wide CI reflects the small sample size in this study. In Matorras et al (Matorras2002) the number of patients who reported recurrence of pain was 4/115 in the estrogen with or without progesterone arm compared with 0/57 women in the no-treatment arm. The result was not significant (OR 4.64, 95% CI 0.25 to 87.71).

### **Confirmed recurrence or exacerbation of endometriosis**

While this outcome was not reported in Fedele (Fedele1999), Matorras et al (Matorras2002) found that 2/115 of the estrogen with or without progesterone group developed recurrence of endometriosis that was confirmed histopathologically. No recurrence was reported in the no-treatment group. This finding was not statistically significant.

### **Cancer diagnosis**

There was no documentation of cancer formation in either study (Fedele1999; Matorras2002).

### **Re-operation for endometriosis**

In the Matorras study (Matorras2002) 2/115 women in the estrogen with or without progesterone group were re-operated on while no woman was re-operated in the no-treatment group. The OR was 2.53 (95% CI 0.12 to 53.64) and was not statistically significant.

### **Mortality**

There was no case of mortality related to the medication reported in either study (Fedele1999; Matorras2002).

## **DISCUSSION**

This review addresses the controversial issue of the use of hormone replacement therapy for women with endometriosis and post-surgical menopause. There were only two randomised controlled studies that addressed this issue (Fedele1999; Matorras2002). Although they used similar inclusion criteria (women with endometriosis who underwent bilateral salpingoophorectomy with or without hysterectomy) the reviewed studies used different comparisons; meta-analysis was, therefore, not feasible.

Both studies have the potential for bias derived from the fact that Fedele et al (Fedele1999) did not apply blinding to the method of intervention and in Matorras (Matorras2002) only the gynaecologist following the women was kept unaware about the method

of treatment. However, both studies had full retention of participants for the duration of follow up, with regular interim reviews as planned in the methodology. In the analysis, statistical heterogeneity was not tested as the studies used different control interventions. Neither study addressed development of cancer or mortality related to the disease after initiation of the treatment.

An assessment of pain recurrence after hormone replacement was difficult. In Fedele et al (Fedele1999) the pain recurrence was classified as either mild, moderate, or severe while in Matorras (Matorras2002) there was no such classification. This pain recurrence may be due to the underlying disease of endometriosis and the amount of residual tissue left after the initial surgery, which raises concerns. We considered the recurrence of pelvic pain and dyspareunia as signs of pain recurrence hence this review demonstrates the effect of hormone replacement therapy for women with endometriosis and post-surgical menopause on recurrence of dysmenorrhoea, dyspareunia, and non-menstrual pelvic pain when compared to tibolone and no treatment.

The recurrence rate of the endometriosis was assessed clinically and by pelvic ultrasonography in Matorras et al (Matorras2002). Both studies followed up the women for at least one year (mean of 45 months in Matorras et al (Matorras2002) and a minimum of 12 months in Fedele (Fedele1999)). There was no significant difference between the hormone replacement groups and the control groups in term of pain recurrence for both studies. As there are only two studies addressing the issue of pain recurrence in women with endometriosis and post-surgical menopause, and both studies have used different control criteria, there is a possibility of publication bias.

In summary there is some evidence from two non-blinded randomised controlled trials that hormone replacement therapy for women with endometriosis and post-surgical menopause may lead to pain and disease recurrence

## **AUTHORS' CONCLUSIONS**

### **Implications for practice**

Hormone replacement therapy for women with endometriosis and post-surgical menopause could result in pain and disease recurrence. However, the evidence in the literature is not strong enough to suggest depriving severely symptomatic patients from this treatment in order to relieve their menopausal symptoms.

There is a need for double-blinded randomised controlled studies to investigate further the effects of hormone replacement therapy on disease and pain recurrence.

### **Implications for research**

Further studies are required to compare the use of different types of hormone replacement therapy in women with endometriosis and post surgical menopause. These studies need to address:

1. recurrence of the disease;
2. recurrence of pain;
3. women's quality of life.

## ACKNOWLEDGEMENTS

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## REFERENCES

### References to studies included in this review

- Fedele 1999** {published data only}  
Fedele L, Bianchi S, Raffaelli R, Zanonato G. Comparison of transdermal estradiol and tibolone for the treatment of oophorectomized women with deep residual endometriosis. *Maturitas* 1999;**32**:189–93.
- Matorras 2002** {published data only}  
Matorras R, Elorriaga MA, Pijoan JI, Ramon O, Rodriguez-Escudero FJ. Recurrence of endometriosis in women with bilateral adnexectomy (with or without total hysterectomy) who received hormone replacement therapy. *Fertility and Sterility* 2002;**77**(2):303–8.

### References to studies excluded from this review

- Alexander 2004** {published data only}  
\* Alexander JL, Kotz K, Dennerstein L, Kutner SJ, Wallen K, Notelovitz M. The effect of postmenopausal hormone therapies on female sexual function: a review of double-blind randomized controlled trials. *Menopause* 2004;**11**(6 part 2):749–65, 786–8.
- Arumugam 1998** {published data only}  
Arumugam K, Damodaran P. Endometriosis and estrogen replacement therapy. *Medical Science Research* 1998;**26**(5):333–4.
- Attar 2006** {published data only}  
Attar E, Bulun SE. Aromatase inhibitors: the next generation of therapeutics for endometriosis?. *Fertility and Sterility* 2006;**85**(5):1307–18.
- Bain 2006** {published data only}  
Bain C. Managing women with a previous diagnosis of endometriosis. *Journal of the British Menopause Society* 2006;**12**(1):28–33.
- Barrett-Connor 2005** {published data only}  
\* Barrett-Connor E, Grady D, Stefanick ML. The rise and fall of menopausal hormone therapy. *Annual Review of Public Health* 2005;**26**:115–40.
- Beard 1991** {published data only}  
Beard RW, Kennedy RG, Gangar KF, Stones RW, Rogers V, Reginald PW, Anderson M. Bilateral oophorectomy and hysterectomy in the

treatment of intractable pelvic pain associated with pelvic congestion. *British Journal of Obstetrics and Gynaecology* 1991;**98**(10):988–92.

- Bianchi 1997** {published data only}  
Bianchi S, Raffaelli R, Borrueto F, Agnoli B, Fedele L. Comparison of transdermal estradiol and tibolone for the treatment of oophorectomized women with residual pelvic endometriosis. *Fertility and Sterility* 1997;**1997**:187.
- Bradshaw 2002** {published data only}  
Bradshaw H. Estrogen replacement reverses ovariectomy-induced vaginal hyperalgesia in the rat. *Maturitas* 2002;**41**(2):157–65.
- Bulun 2005** {published data only}  
Bulun SE, Imir G, Utsunomiya H, Thung S, Gurates B, Tamura M, Lin Z. Aromatase in endometriosis and uterine leiomyomata. *Journal of Steroid Biochemistry and Molecular Biology* 2005;**95**(1–5):57–62.
- Chalas 2005** {published data only}  
Chalas E, Costantino JP, Wickerham DL, Wolmark N, Lewis GC, Bergman C, Runowicz CD. Benign gynecologic conditions among participants in the Breast Cancer Prevention Trial. *American Journal of Obstetrics and Gynecology* 2005;**192**(4):1230–9.
- Colau 2007** {published data only}  
\* Colau JC. The genitourinary disorders of the menopause. Role of hormonal treatment. *Reproduction Humaine et Hormones* 2007;**20**(5):300–5.
- Davis 2003** {published data only}  
Davis CJ, McMillan L. Pain in endometriosis: Effectiveness of medical and surgical management. *Current Opinion in Obstetrics and Gynecology* 2003;**15**(6):507–12.
- Dennerstein 1980** {published data only}  
\* Dennerstein L, Burrows GD, Hyman GJ, Sharpe K. Some clinical effects of oestrogen and progestogen. *Maturitas* 1980;**2**(1):19–28.
- Dowsett 2005** {published data only}  
Dowsett M, Folkard E, Doody D, Haynes B. The biology of steroid hormones and endocrine treatment of breast cancer. *Breast* 2005;**14**(6):452–7.

- Farquhar 2006** {published data only}  
 \* Farquhar C, Latthe P. Chronic pelvic pain: Aetiology and therapy. *Review in Gynaecological and Perinatal Practice* 2006;**6**(3-4):117–84.
- Fedele 2005** {published data only}  
 Fedele L, Bianchi S, Zanonato G, Berlanda N, Borruto F, Frontino G. Tailoring radicality in demolitive surgery for deeply infiltrating endometriosis. *American Journal Of Obstetrics and Gynecology* 2005; **193**(1):114–7.
- Frackiewicz 2003** {published data only}  
 Frackiewicz EJ, Zarotsky V. Diagnosis and treatment of endometriosis. *Expert Opinion on Pharmacotherapy* 2003;**4**:67–82.
- Friedlander 2002** {published data only}  
 Friedlander AH. Dentistry & medicine. The physiology, medical management and oral implications of menopause. *Journal of the American Dental Association* 2002;**133**(1):73-81, 89-92.
- Ghezzi 2005** {published data only}  
 Ghezzi F, Cromi A, Colombo G, Uccella S, Bergamini V, Serati M. Minimizing ancillary ports size in gynecologic laparoscopy: A randomized trial. *Journal of Minimally Invasive Gynecology* 2005;**12**(6): 480–5.
- Goulding 1991** {published data only}  
 Goulding A, Fisher L. Preventive effects of clomiphene citrate on estrogen-deficiency osteopenia elicited by LHRH agonist administration in the rat. *Journal of Bone and Mineral Research* 1991;**6**(11): 1177–81.
- Graziottin 2007** {published data only}  
 Graziottin A. Effect of primary menopause on sexuality. *Women's Health* 2007;**3**(4):455–74.
- Hackman 1997** {published data only}  
 Hackman BW, Galbraith D. Six months pilot study of oestrogen replacement therapy with piperazine oestrone sulphate and its effect on memory. *Current Medical Research and Opinion* 1997;**4**:21–8.
- Hansen 2006** {published data only}  
 Hansen KA, Eyster KM. A review of current management of endometriosis in 2006: an evidence-based approach. *South Dakota Medicine: The Journal of the South Dakota State Medical Association* 2006;**59**(4):153–9.
- Holub 2000** {published data only}  
 \* Holub Z, Voracek J, Wagnerova M, Kliment L. Hormone replacement therapy in women with surgical treatment of endometriosis and adenomyosis: prospective and follow-up study. part I [Hormonalni substitucni lecba u zen operovanych pro endometrioziu a adenomyozu: prospektivni follow-up studie. I. Cast]. *Ceskoslovenska Gynecologie/Ceska lekarska spolecnost J Ev Purkyne* 2000;**65**(1):16–20.
- Holub 2001** {published data only}  
 Holub Z, Brozkova H, Kucera M, Krackova J, Martinovska M, Muller M, et al. Hormonal substitution treatment in women operated on account of endometriosis and adenomyosis: Prospective follow-up study (part II). [Hormonalni substitucni lecba u zen operovanych pro endometrioziu a adenomyozu – prospektivni follow-up studie (II. cast).]. *Ceskoslovenska Gynecologie* 2001;**66**(6):405–8.
- Hu W-P 2006** {published data only}  
 Hu W-P, Sun KT, Zhao Y. Endometriosis-specific genes identified by real-time reverse transcription-polymerase chain reaction expression profiling of endometriosis versus autologous uterine endometrium. *Journal of Clinical Endocrinology and Metabolism* 2006;**91**(1):228–38.
- Ivanov 1998** {published data only}  
 Ivanov S, Ivanov S. Malignant degeneration in women operated on for endometriosis. *Akusherstvo i Ginekologija* 1998;**37**(3):29–30.
- Jelovsek 2004** {published data only}  
 Jelovsek JE, Winans C, Brainard J, Falcon T. Endometriosis of the liver containing mullerian adenosarcoma: case report. *American Journal of Obstetrics and Gynecology* 2004;**191**(5):1725–7.
- Johnson 2006** {published data only}  
 Johnson N. Management of dysmenorrhea. *Reviews in Gynaecological and Perinatal Practice*. 2006;**6**(1-2):57–62.
- Jones 2002** {published data only}  
 Jones KD, Owen E, Berresford A, Sutton C. Endometrial adenocarcinoma arising from endometriosis of the rectosigmoid colon. *Gynecologic Oncology* 2002;**86**(2):220–2.
- Jordan 2003** {published data only}  
 Jordan SJ, Purdie DM, Whiteman DC, Webb PM. Risk factors for epithelial ovarian cancer. *Cancer Forum* 2003;**23**(3):148–51.
- Kenemans 2005** {published data only}  
 Kenemans P, Speroff L. Tibolone: Clinical recommendations and practical guidelines: A report of the International Tibolone Consensus Group. *Maturitas* 2005;**51**(1):21–8.
- Khastgir 1998** {published data only}  
 Khastgir G. Hysterectomy, ovarian failure and depression. *Menopause* 1998;**5**(2):113–22.
- Kiesel 2002** {published data only}  
 Kiesel LA, Rody A, Greb RR, Szilagyi A. Clinical use of GnRh analogues. *Clinical Endocrinology* 2002;**56**(6):677–87.
- Kitawaki 2001** {published data only}  
 Kitawaki J, Obayashi H, Ishihara H, Koshiba H, Kusuki I, Kado N, et al. Estrogen receptor-alpha gene polymorphism is associated with endometriosis, adenomyosis and leiomyomata. *Human Reproduction* 2001;**16**(1):51–5.
- Kouides 2006** {published data only}  
 Kouides PA. Current understanding of von Willebrand's disease in women - Some answers, more questions. *Haemophilia* 2006;**12**(3): 143–51.
- Kroon 2005** {published data only}  
 Kroon N, Reginald P. Medical management of chronic pelvic pain. *Current Obstetrics and Gynaecology* 2005;**15**(5):285–90.
- Kuenzel 2006** {published data only}  
 Kuenzel W. Editors' highlights. *European Journal of Obstetrics and Gynecology* 2006;**129**(2):101–3.
- Kuohung 2002** {published data only}  
 Kuohung W, Jones GL, Vitonis AF, Cramer DW, Kennedy SH, Thomas D, Hornstein MD. Characteristics of patients with endometriosis in the United States and the United Kingdom. *Fertility and Sterility* 2002;**78**(4):767–72.
- Kuzel 1999** {published data only}  
 \* Kuzel D, Fucikova Z, Toth D, Cibula D, Zivny J. Endometrial ablation: prospective 3-year follow-up study. *Ceskoslovenska Gynecologic* 1999;**64**(2):87–9.

- Lalchandani 2005** {published data only}  
Lalchandani S, Baxter A, Philips K. Is helium thermal coagulator therapy for the treatment of women with minimal to moderate endometriosis cost-effective? prospective randomised controlled trial. *Gynecological Surgery* 2005;**2**(4):255–8.
- Leyendecker 2002** {published data only}  
Leyendecker G, Herbertz M, Kunz G, Mall G. Endometriosis results from the dislocation of basal endometrium. *Human Reproduction* 2002;**17**(10):2725–36.
- Lobo 1984** {published data only}  
\* Lobo RA, McCormick W, Singer F, Roy S. Depo-Medroxyprogesterone acetate compared with conjugated estrogens for the treatment of post menopausal woman. *Obstetrics and Gynecology* 1984;**63**(1):1–5.
- Loizzi 2005** {published data only}  
Loizzi V, Cormio G, Vicino M, Fattizzi N, Bettocchi S, Selvaggi L. Hormone replacement therapy on ovarian and uterine cancer risk and cancer survivors: How shall we do no harm?. *International Journal of Gynecological Cancer* 2005;**15**(3):420–5.
- Long 2006** {published data only}  
Long CY, Liu CM, Hsu SC, Wu CH, Wang CL, Tsai EM. A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women. *Menopause* 2006;**13**(5):737–43.
- Lopez-Olmos 2003** {published data only}  
Lopez-Olmos J. Sexuality following the menopause: The influence of hormone replacement therapy on women with sexual dysfunction. *Clinica e Investigacion en Ginecologia y Obstetricia* 2003;**30**(7):212–21.
- Lu 1995** {published data only}  
Lu PY, Ory SJ. Endometriosis: current management. *Mayo Clinic Proceedings* 1995;**70**(5):453–63.
- Luciano 2006** {published data only}  
Luciano DE, Luciano AA. Pain associated with endometriosis: Therapeutic options. *Women's Health* 2006;**2**(4):617–26.
- Mannix 2004** {published data only}  
\* Mannix LK, Calhoun AH. Menstrual migraine. *Current Treatment Options in Neurology* 2004;**6**(6):489–98.
- Mendoza 2000** {published data only}  
Menodza N, Suarez AM, Alamo F, Bartual E, Vergara F, Herruzo A. Lipid effects, effectiveness and acceptability of tibolone versus transdermic 17beta-estradiol for hormonal replacement therapy in women with surgical menopause. *Maturitas* 2000;**37**(1):37–43.
- Mizutani 1995** {published data only}  
Mizutani T, Nishiyama S, Amakawa I, Watanabe A, Nakamuro K, Terada N. Danazol concentrations in ovary, uterus, serum and their effect on the hypothalamic-pituitary-ovarian axis during vaginal administration of a danazol suppository. *Fertility and Sterility* 1995;**63**(6):1184–9.
- Modugno 2003** {published data only}  
Modugno F, Boyd J, Baum A, Bigbee WL, Cramer D, Ferrell R, et al. Ovarian cancer and high risk women - implications for prevention, screening and early detection. *Gynecologic Oncology* 2003;**91**(1):15–31.
- Moen 2002** {published data only}  
Moen MH, Stokstad T. A long term follow-up study of women with symptomatic endometriosis diagnosed incidentally at sterilization. *Fertility and Sterility* 2002;**78**(4):773–6.
- Morini 1993** {published data only}  
Morini A, Aleandri V, Cantonetti G, Benagiano G. Directions of future research on GnRh analogs in the treatment of endometriosis and uterine fibromyoma. *Minerva Ginecologica* 1993;**45**(10):455–65.
- Mousa 2007** {published data only}  
Mousa NA, Bedaiwy MA, Casper RF. Aromatase inhibitors in the treatment of severe endometriosis. *Obstetrics and Gynecology* 2007;**109**(6):1421–3.
- Murphy 1995** {published data only}  
Murphy AA, Kettle LM, Morales AJ, Roberts V, Parmley T, Yen SS. Endometrial effects of long-term low-dose administration of RU486. *Fertility and Sterility* 1995;**63**(4):76.
- Nagao 2006** {published data only}  
Nagao S, Fujiwara K, Ishikawa H, Oda T, Tanaka K, Aotani E, Kohano I. Hormonal function after ovarian transposition to the abdominal subcutaneous fat tissue. *International Journal of Gynecological Cancer* 2006;**16**(1):121–4.
- Nagata 2001** {published data only}  
Nagata C, Takatsuka N, Kawakami N, Shimizu H. Soy product intake and premenopausal hysterectomy in a follow-up study of a Japanese women. *European Journal of Clinical Nutrition* 2001;**55**(9):773–7.
- Namnoum 1995** {published data only}  
Namnoum AB, Hickman TN, Goodman SB, Gehbach DL, Rock JA. Incidence of symptom recurrence after hysterectomy for endometriosis. *Fertility and Sterility* 1995;**64**(5):898–902.
- Nappi 2006** {published data only}  
\* Nappi R, Wawra K, Schmitt S. Hypoactive sexual desire disorder in post menopausal women. *Gynecological Endocrinology* 2006;**22**(6):318–23.
- Nasir 2004** {published data only}  
\* Nasir L, Bope ET. Management of pelvic pain from dysmenorrhea or endometriosis. *Journal of the American Board of Family Practice* 2004;**17**(1):43–7.
- Noble 1979** {published data only}  
Nobel AD, Letchworth AT. Medical treatment of endometriosis: A comparative trial. *Postgraduate Medical Journal* 1979;**55**(5):37–9.
- Ozawa 2006** {published data only}  
Ozawa Y, Murakami T, Terada Y, Yaegashi N, Okamura K, Kuriyama S, Tsuji I. Management of pain associated with endometriosis: An update of the painful problems. *Tohoku Journal of Experimental Medicine* 2006;**210**(3):175–88.
- Ozols 2004** {published data only}  
\* Ozols RF, Bookman MA, Connolly DC, Daly MB, Godwin AK, Schilder RJ, et al. Focus in epithelial ovarian cancer. *Cancer Cell* 2003;**5**(1):19–24.
- Perry 1996** {published data only}  
Perry CM, Brogden RN. Goserelin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in benign gynaecological disorders. *Drugs* 1996;**51**(2):319–46.

**Piltonen 2002** {published data only}

Piltonen T, Koivunen R, Morin-Papunen L, Ruokonen A, Huh-taniemi IT, Tapanainen JS. Ovarian and adrenal steroid production: Regulatory role of LH/HCG. *Human Reproduction* 2002;**17**(3):620–4.

**Pruthi 2007** {published data only}

\* Pruthi S, Brandt KR, Degnim AC, Goetz MP, Perez EA, Reynolds CA, et al. A multidisciplinary approach to the management of breast cancer, part 1: Prevention and diagnosis. *Mayo Clinic Proceedings* 2007;**82**(8):999–1012.

**Purdie 1999** {published data only}

Purdie DM, Bain CJ, Siskind V, Russell P, Hacker NF, Ward BG, et al. Hormone replacement therapy and risk of epithelial ovarian cancer. *British Journal of Cancer* 1999;**81**(3):559–63.

**Rattanachaiyanont 03** {published data only}

Rattanachaiyanont M, Angsuwatthana S, Inthawiwat S, Tanma-hasamut P, Techatraisak K, Leerasiri P. Hormonal replacement therapy in surgical menopause with underlying endometriosis. *Journal of the Medical Association of Thailand* 2003;**86**(8):702–7.

**Rees 2006** {published data only}

\* Rees M. Gynecological oncology prospective on management of the menopause. *European Journal of Surgical Oncology* 2006;**32**(8): 892–7.

**Reid 1996** {published data only}

Reid BA, Gangar KF, Rogers V, Thomas E, Beard RW. Long-term results of bilateral oophorectomy for the treatment of chronic pelvic pain: Relief of pain and special hormone replacement therapy requirements. *Journal of Obstetrics and Gynecology* 1996;**16**(6):538–43.

**Robson 2003** {published data only}

Robson M, Hensley M, Barakat R, Brown C, Chi D, Poynor E, Offit K. Quality of life in women at risk for ovarian cancer who have undergone risk-reducing oophorectomy. *Gynecologic Oncology* 2003;**89**(2):281–7.

**Roman 2007** {published data only}

\* Roman H. Guidelines for the management of painful endometriosis. *Journal de Gynecologie Obstetrique et Biologie de la Reproduction* 2007;**36**(2):141–50.

**Rotella 2006** {published data only}

\* Rotella D. COMP - structure-based design and development of estrogen receptor. *IDrugs* 2006;**9**(11):748–50.

**Santos Gonzalez 2001** {published data only}

Santos Gonzalez JE. Treatment of early menopause. *Revisita de Iberoamericana de Revisiones en Menopausia* 2001;**3**(2):15–8.

**Schor 1999** {published data only}

Schor E, Barakat EC, Simoes MJ, De Freitas V, Giannotti Filho O, Rodrigues De Lima G. Effects of conjugated estrogens and progesterone in surgically induced endometriosis in oophorectomized rats. *Clinical and Experimental Obstetrics and Gynecology* 1999;**26**(3-4): 158–61.

**Schwenkhagen 2006** {published data only}

Schwenkhagen A. When libido stops. *MMW Fortschritte der Medizin* 2006;**148**(25):54–5.

**Setnikar 1997** {published data only}

Sitnikar I, Rovati LC, Thebault JJ, Guillaume M, Mignot A, Renoux A, Gualano V. Pharmacokinetics of estradiol and of estrone during application of three strengths of an estradiol transdermal patch with active matrix. *Arzneimittel-Forschung/Drug Research* 1997;**47**(7):859–65.

**Tan 2008** {published data only}

\* Tan SH, Wolff AC. *Current Oncology Reports* 2008;**10**(1):27–37.

**Tietjen 2006** {published data only}

\* Tietjen GE, Conway A, Utley C, Gunning WT, Herial NA. Migraine is associated with menorrhagia and endometriosis. *Headache* 2006;**46**(3):422–8.

**Tok 2006** {published data only}

Tok EC, Ertunc D, Tataroglu C, Yazici G, Kanat H, Dilek S. Clinicopathologic study of gynecological cancer. *International Journal of Gynecological Cancer* 2006;**16**(2):501–6.

**Uemura 2000** {published data only}

Uemura H, Irahara M, Yoneda N, Yasui T, Genjida K, Miyamoto KL, et al. Close correlation between estrogen treatment and renal phosphate reabsorption capacity. *Journal of Clinical Endocrinology and Metabolism* 2000;**85**(3):1215–9.

**Usman 2008** {published data only}

\* Usman SB, Indusekhar R, O' Brien S. Hormonal management of premenstrual syndrome. *Best Practice and Research in Clinical Obstetrics and Gynaecology* 2008;**22**(2):251–60.

**Varma 2006** {published data only}

Varma R, Sinha D, Gupta JK. Non-contraceptive uses of levonorgestrel-releasing hormone system (LNG-IUS) - A systematic enquiry and overview. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2006;**125**(1):9–28.

**Velasco 2006** {published data only}

Velasco I, Rueda J, Acien P. Aromatase expression in endometriotic tissues and cell cultures of patients with endometriosis. *Molecular Human Reproduction* 2006;**12**(6):377–81.

**Vercellini 2008** {published data only}

\* Vercellini P, Somigliana E, Vignani P, Abbiati A, Daguati R. Endometriosis: current and future medical therapies. *Best Practice and Research in Clinical Obstetrics and Gynaecology* 2008;**22**(2):275–306.

**Walker 2005** {published data only}

Walker ID. Hormone replacement therapy and venous thrombolism. *Thrombosis Research* 2005;**115**:88–92.

**Weiss 1982** {published data only}

\* Weiss NS, Lyon JL, Krishnamurthy S, Dietert SE, Liff JM, Darling JR. Noncontraceptive estrogen use and the occurrence of ovarian cancer. *Journal of the National Cancer Institute* 1982;**68**(1):95–8.

**Winkel 2001** {published data only}

\* Winkel CA, Scialli AR. Medical and surgical therapies for pain associated with endometriosis. *Journal of Women Health & Gender-Based Medicine* 2001;**10**(2):137–62.

**Wolff 1982** {published data only}

\* Wolff JP, Cachelou R, Gueritee N. Absence of systematic hormonal effects in an oestradiol diether topically active on the vaginal mucosa. *Maturitas* 1982;**4**(4):239–46.

**Wolff 1983** {published data only}

Wolff JP, Cachelou R. Sexual problems secondary to gynaecological cancer. Their local treatment by an estradiol diether devoid of systemic hormonal activity. *Revue Francaise de Gynecologie et d'Obstetrique* 1983;**78**(3):189–94.

**Wylie 2006** {published data only}

\* Wylie KR. Sexuality and the menopause. *Journal of the British Menopause Society* 2006;**12**(4):149–52.

**Yohannes 2003** {published data only}

Yohannes P. Ureteral endometriosis. *Journal of Urology* 2003;**170**(1):20–5.

**Additional references**

**Agarwal 2002**

Agarwal SK. Impact of six months of GnRH agonist therapy for endometriosis. Is there an age-related effect on bone mineral density?. *The Journal of Reproductive Medicine* 2002;**47**(7):530–4.

**Belchetz 1994**

Belchetz PE. Hormonal treatment of postmenopausal women. *The New England Journal of Medicine* 1994;**330**(15):1062–71.

**Bruner-Tran 2002**

Bruner-Tran KL, Webster-Clair D, Osteen KG. Experimental endometriosis: the nude mouse as a xenographic host. *Annals of the New York Academy of Science* 2002;**955**:328–39.

**Cedars 1990**

Cedars M, Lu J, Meldrum D, Judd H. Treatment of endometriosis with a long acting gonadotropin-releasing hormone agonist plus medroxy-progesterone acetate. *Obstetrics and Gynaecology* 1990;**75**:641–5.

**Chatman 1982**

Chatman DL, Ward AB. Endometriosis in adolescents. *Journal of Reproductive Medicine* 1982;**27**:156.

**Donnez 1997**

Donnez J, Nisolle M, Gillerot S, et al. Rectovaginal septum adenomyotic nodules: a series of 500 cases. *British Journal of Obstetrics and Gynaecology* 1997;**104**(9):1014–8.

**Fedele 2004**

Fedele L, Bianchi S, Zanonato G, et al. Is rectovaginal endometriosis a progressive disease?. *American Journal of Obstetrics and Gynaecology* 2004;**191**(5):1539–42.

**Haney 1991**

Haney AF. The pathogenesis and etiology of endometriosis. In: Thomas E, Rock J editor(s). *Modern Approaches to Endometriosis*. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1991:3–19.

**Kitawaki 2002**

Kitawaki J, Kado N, Koshiha H, Honjo H. Endometriosis: the pathophysiology as an estrogen-dependant disease. *Journal of Steroid Biochemistry and Molecular Biology* 2002;**83**(1–5):149–55.

**Lindsay 1996**

Lindsay PC, Show RW, Bennink HJ, Kicovic P. The effect of add-back treatment with tibolone (Livial) on patient treated with

gonadotropin-releasing hormone against triptorelin (Decapeptide). *Fertility and Sterility* 1996;**65**:342–83.

**Makarainen 1996**

Makarainen L, Ronneberg L, Kauppila A. Medroxyprogesterone acetate supplementation diminishes the hypo-estrogenic side effects of gonadotropin-releasing hormone agonists without changing its efficacy in endometriosis. *Fertility and Sterility* 1996;**65**:29–34.

**Matorras 2002**

Matorras R, Elorriaga MA, Pijoan JI, Ramon O. Recurrence of endometriosis in women with bilateral adnexectomy (with or without total hysterectomy) who received hormone replacement therapy. *Fertility and Sterility* 2002;**77**(2):303–8.

**Riis 1990**

Riis B, Christiansen C, Johansen J, Jacobson J. Is it possible to prevent one loss in young women treated with luteinizing hormone-releasing hormone agonist?. *Journal of Clinical Endocrinology and Metabolism* 1990;**70**:920–4.

**Rock 1992**

Rock JA, Moutos DM. Endometriosis: the present and the future - an overview of treatment options. *British Journal of Obstetrics and Gynaecology* 1992;**99** Suppl 7:1–4.

**Sagsveen 2003**

Sagsveen M, Farmer JE, Prentice A, Breeze A. Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD001297]

**Sangi-Haghepykar 1995**

Sangi-Haghepykar H, Poindexter AN. Epidemiology of endometriosis among parous women. *Obstetrics and Gynaecology* 1995;**85**:983.

**Shaw 1992**

Shaw RW. Treatment of endometriosis. *Lancet* 1992;**340**:1267–71.

**Slenvenson 1989**

Slenvenson JC, Lee B, Gardner R, Shaw RW. A comparison of the skeletal effects of goserlin and danazol in premenopausal women with endometriosis. *Hormone Research* 1989;**32**:161–4.

**Surrey 1990**

Surrey ES, Gambone JC, Lu JKH, Judd HL. The effects of combining norethindrone with a gonadotropin-releasing hormone agonist in the treatment of symptomatic endometriosis. *Fertility and Sterility* 1990;**53**:620–6.

**Surrey 1992**

Surrey E, Judd H. Reduction of vasomotor symptoms and bone mineral density loss with combined norethindrone and long acting gonadotropin-releasing hormone agonist therapy of symptomatic endometriosis: a prospective randomized trial. *Journal of Clinical Endocrinology and Metabolism* 1992;**75**:558–63.

**Tabkin 1997**

Tabkin O, Yakinoghe AH, Kucuk S, Uryan I, Buhur A, Burak F. Effectiveness of tibolone on hypo-estrogenic symptoms induced by goserelin treatment in patients with endometriosis. *Fertility and Sterility* 1997;**67**:40–5.

\* Indicates the major publication for the study



## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Fedele1999

Methods	RCT Computer-generated randomization.	
Participants	Symptomatic patients with deeply infiltrating endometriotic nodules that recurred after one or more previous operations. Patients had bilateral oophorectomy with or without hysterectomy. The disease was not completely eradicated after the surgery.	
Interventions	Nonstop transdermal 17 $\beta$ -estradiol 0.05 mg/d combined with cyclic medroxy progesterone acetate 10 mg/d for12 days/month in women with conserved uterus Control: nonstop tibolone 2.5 mg/d.	
Outcomes	Pain as reported by the patients at 3, 6, and 12 months after the start of the treatment.	
Notes	The duration of the treatment was at least 12 months. All women were followed for 12 months and no participant suspended the therapy which indicates that intention to treat analysis was applied. There was no blinding as the method of intervention and the control were different.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization was computer generated
Allocation concealment?	Unclear	Unclear, the method was not mentioned
Blinding? All outcomes	No	The intervention and control were different
Incomplete outcome data addressed? All outcomes	Yes	The reported outcome was clear: pain as reported by the patient at 3, 6, and 12 months after the start of the treatment
Free of selective reporting?	Yes	The reported outcome was clear and as planned in the methodology
Free of other bias?	Yes	Apart from blinding's and allocation concealment, there was no other bias

**Matorras2002**

Methods	RCT The randomization was done using sealed envelopes. The randomization was done by a person not connected to the study.
Participants	Women with histological diagnosis of endometriosis in whom BSO was done irrespective of associated surgical procedures. No hormonal treatment during 6-month period before surgery. No medical treatment of endometriosis.
Interventions	Sequential administration of estrogen and progesterone following Belchetz's criteria Two 22 cm <sup>2</sup> patches were applied per week which produced a controlled release of 50 microgram/day. Micronized progesterone was administered orally during 14 days, 200 mg/24 hours, with a 16-day interval free of treatment.
Outcomes	Recurrence of endometriosis that was diagnosed based on histological study, clinical findings, and ultrasound findings suggestive of endometriosis.
Notes	There was no placebo but the women were all monitored by the same gynaecologist who was kept unaware of their treatment status.

***Risk of bias***

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	The randomization was done using sealed envelopes
Allocation concealment?	Yes	Adequate, randomization was done by a person not related to the study
Blinding? All outcomes	No	There was no blinding except for the assessing gynaecologist who was kept unaware of treatment status
Incomplete outcome data addressed? All outcomes	Yes	There was a clearly addressed outcome: recurrence of endometriosis that was diagnosed based on histological study, clinical findings, and ultrasound findings suggestive of endometriosis
Free of selective reporting?	Yes	The report included the selected outcome
Free of other bias?	Yes	Apart from blinding, no other bias identified

**Characteristics of excluded studies** *[ordered by study ID]*

Alexander 2004	Unrelated topic
Arumugam 1998	No randomization
Attar 2006	Unrelated topic
Bain 2006	Unrelated topic Review and not RCT
Barrett-Connor 2005	Unrelated topic
Beard 1991	Unrelated topic Not RCT
Bianchi 1997	Part of Fedele 1999 study that was included
Bradshaw 2002	Unrelated topic
Bulum 2005	Unrelated topic
Chalas 2005	Unrelated topic
Colau 2007	Unrelated topic
Davis 2003	Unrelated topic
Dennerstein 1980	Unrelated topic
Dowsett 2005	Unrelated topic Not RCT
Farquhar 2006	Unrelated topic
Fedele 2005	Unrelated topic Not RCT
Frackiewicz 2003	Unrelated topic
Friedlander 2002	Unrelated topic Not RCT
Ghezzi 2005	Unrelated topic

(Continued)

Goulding 1991	Unrelated topic
Graziottin 2007	Unrelated topic
Hackman 1997	Unrelated topic
Hansen 2006	Unrelated topic Not RCT
Holub 2000	No appropriate randomization
Holub 2001	No appropriate randomization
Hu W-P 2006	Unrelated topic
Ivanov 1998	Not RCT
Jelovsek 2004	Unrelated topic Not RCT
Johnson 2006	Unrelated topic Not RCT
Jones 2002	Unrelated topic Not RCT
Jordan 2003	Unrelated topic
Kenemans 2005	Unrelated topic Not RCT
Khastgir 1998	Unrelated topic
Kiesel 2002	Unrelated topic
Kitawaki 2001	Unrelated topic Not RCT
Kouides 2006	Unrelated topic
Kroon 2005	Unrelated topic Not RCT
Kuenzel 2006	Unrelated topic Editors' highlight

(Continued)

Kuohung 2002	Unrelated topic Not RCT
Kuzel 1999	Unrelated topic
Lalchandani 2005	Unrelated topic
Leyendecker 2002	Unrelated topic
Lobo 1984	Unrelated topic
Loizzi 2005	Unrelated topic Not RCT
Long 2006	Unrelated topic
Lopez-Olmos 2003	Unrelated topic
Lu 1995	Unrelated topic
Luciano 2006	Unrelated topic
Mannix 2004	Unrelated topic
Mendoza 2000	Unrelated topic
Mizutani 1995	Unrelated topic
Modugno 2003	Unrelated topic
Moen 2002	Unrelated topic Not RCT
Morini 1993	Unrelated topic Not RCT
Mousa 2007	Unrelated topic
Murphy 1995	Unrelated topic Not RCT
Nagao 2006	Unrelated topic
Nagata 2001	Unrelated topic Not RCT

(Continued)

Namnoum 1995	Unrelated topic
Nappi 2006	Unrelated topic
Nasir 2004	Unrelated topic
Noble 1979	Unrelated topic
Ozawa 2006	Unrelated topic Not RCT
Ozols 2004	Unrelated topic
Perry 1996	Unrelated topic Not RCT
Piltonen 2002	Unrelated topic
Pruthi 2007	Unrelated topic
Purdie 1999	Unrelated topic Not RCT
Rattanachaiyanont 03	Not RCT
Rees 2006	Unrelated topic
Reid 1996	Unrelated topic
Robson 2003	Unrelated topic
Roman 2007	Unrelated topic
Rotella 2006	Unrelated topic
Santos Gonzalez 2001	Unrelated topic Not RCT
Schor 1999	Unrelated topic
Schwenkhagen 2006	Unrelated topic
Setnikar 1997	Unrelated topic
Tan 2008	Unrelated topic

(Continued)

Tietjen 2006	Unrelated topic
Tok 2006	Unrelated topic
Uemura 2000	Unrelated topic Not RCT
Usman 2008	Unrelated topic
Varma 2006	Unrelated topic Not RCT
Velasco 2006	Unrelated topic
Vercellini 2008	Unrelated topic
Walker 2005	Unrelated topic
Weiss 1982	Unrelated topic Not RCT
Winkel 2001	Unrelated topic Not RCT
Wolff 1982	Unrelated topic
Wolff 1983	Unrelated topic
Wylie 2006	Unrelated topic
Yohannes 2003	Unrelated topic

## DATA AND ANALYSES

### Comparison 1. Estrogen with or without progesterone versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients reporting pain	1	172	Odds Ratio (M-H, Fixed, 95% CI)	4.64 [0.25, 87.71]
2 Recurrence confirmed by histopathology	1	172	Odds Ratio (M-H, Fixed, 95% CI)	2.53 [0.12, 53.64]
3 Re-operation	1	172	Odds Ratio (M-H, Fixed, 95% CI)	2.53 [0.12, 53.64]

### Comparison 2. Estrogen with or without progesterone versus tibolone

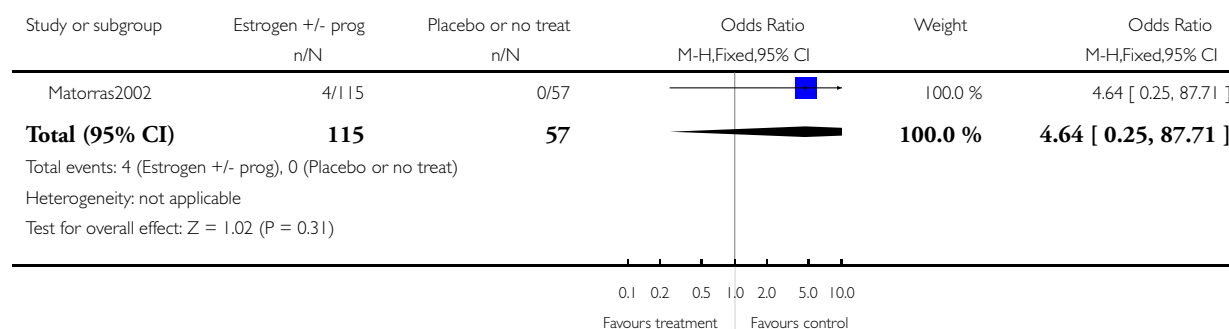
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients reporting pain	1	21	Odds Ratio (M-H, Fixed, 95% CI)	6.67 [0.60, 74.51]

#### Analysis 1.1. Comparison 1 Estrogen with or without progesterone versus placebo or no treatment, Outcome 1 Number of patients reporting pain.

Review: Hormone therapy for endometriosis and surgical menopause

Comparison: 1 Estrogen with or without progesterone versus placebo or no treatment

Outcome: 1 Number of patients reporting pain



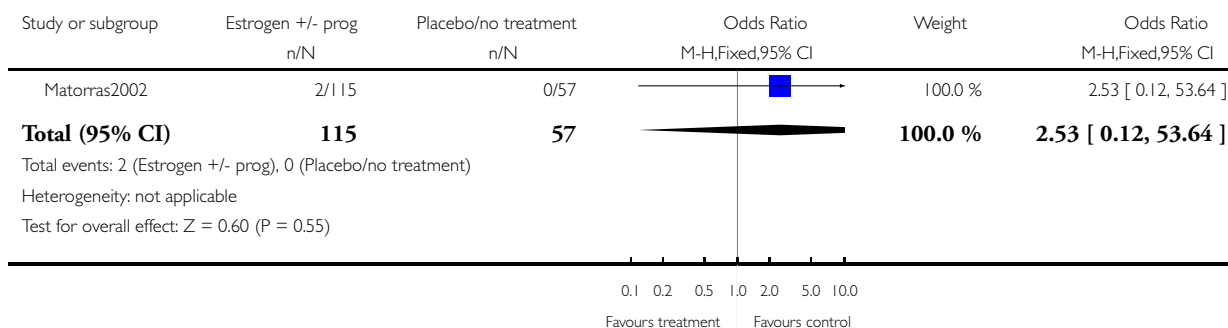


## Analysis 1.2. Comparison 1 Estrogen with or without progesterone versus placebo or no treatment, Outcome 2 Recurrence confirmed by histopathology.

Review: Hormone therapy for endometriosis and surgical menopause

Comparison: 1 Estrogen with or without progesterone versus placebo or no treatment

Outcome: 2 Recurrence confirmed by histopathology

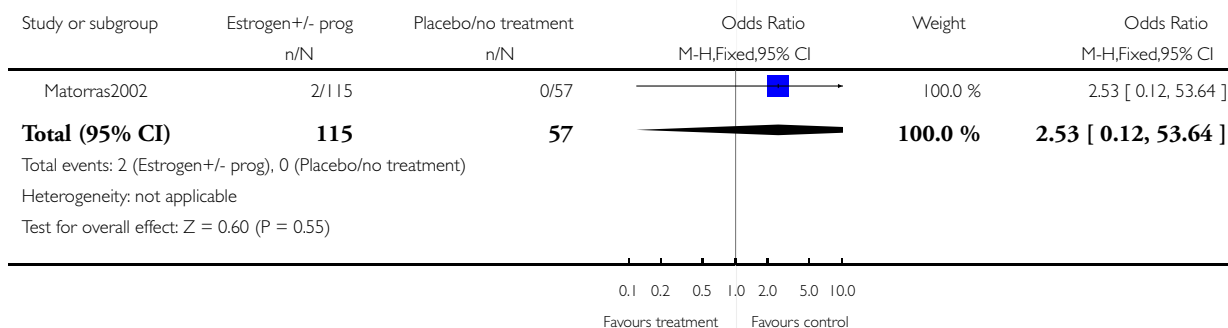


## Analysis 1.3. Comparison 1 Estrogen with or without progesterone versus placebo or no treatment, Outcome 3 Re-operation.

Review: Hormone therapy for endometriosis and surgical menopause

Comparison: 1 Estrogen with or without progesterone versus placebo or no treatment

Outcome: 3 Re-operation

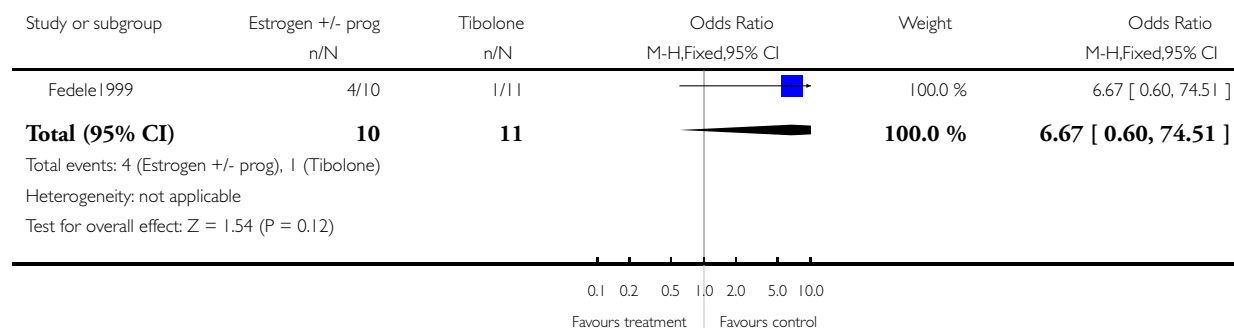


## Analysis 2.1. Comparison 2 Estrogen with or without progesterone versus tibolone, Outcome 1 Number of patients reporting pain.

Review: Hormone therapy for endometriosis and surgical menopause

Comparison: 2 Estrogen with or without progesterone versus tibolone

Outcome: 1 Number of patients reporting pain



## APPENDICES

### Appendix I. MEDLINE

#### MEDLINE search strategy (1950 to 18 March 2008)

- 1 exp Endometriosis/ (12393)
- 2 Endometriosis.tw. (10555)
- 3 exp Pelvic Pain/ (4372)
- 4 (Pelvic adj2 Pain).tw. (3537)
- 5 Dyspareunia/ (938)
- 6 Dyschezia\$.tw. (98)
- 7 Dyspareunia\$.tw. (1433)
- 8 (pain\$ adj2 bowel movement\$).tw. (40)
- 9 exp Ovariectomy/ (15381)
- 10 Ovariectom\$.tw. (17565)
- 11 oophorect\$.tw. (4897)
- 12 (remov\$ adj2 ovar\$).tw. (772)
- 13 (salpingo adj ovariectomy).tw. (7)
- 14 (surgic\$ adj3 menopause).tw. (504)
- 15 or/1-8 (20739)
- 16 or/9-14 (27561)
- 17 15 and 16 (626)
- 18 exp hormone replacement therapy/ or exp estrogen replacement therapy/ (16022)
- 19 (Hormone adj2 therap\$).tw. (15598)
- 20 HRT.tw. (5476)
- 21 Tibolone.tw. (640)
- 22 exp Estrogens/ (120957)
- 23 exp Progesterone/ (56827)
- 24 (Estrogen\$ or Progest\$).tw. (120763)
- 25 or/18-24 (210538)
- 26 17 and 25 (173)

27 randomised controlled trial.pt. (251334)  
 28 controlled clinical trial.pt. (77422)  
 29 randomised controlled trials as topic/ (53023)  
 30 random allocation/ (60395)  
 31 double blind method/ (96065)  
 32 single blind method/ (11789)  
 33 or/27-32 (424467)  
 34 animals/ not (animals/ and humans/) (3189559)  
 35 33 not 34 (397756)  
 36 clinical trial.pt. (446433)  
 37 exp clinical trials as topic/ (201557)  
 38 (clinic\$ adj25 trial\$).ti.ab. (142061)  
 39 cross-over studies/ (21493)  
 40 (crossover or cross-over or cross over).tw. (40169)  
 41 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti.ab. (95360)  
 42 placebos/ (26962)  
 43 placebo\$.ti.ab. (108242)  
 44 random\$.ti.ab. (401463)  
 45 research design/ (51618)  
 46 or/36-45 (910204)  
 47 46 not 34 (843399)  
 48 35 or 47 (865071)  
 49 26 and 48 (14)  
 50 from 49 keep 1-14 (14)

## Appendix 2. Psych INFO

1 exp Endometriosis/ (0)  
 2 Endometriosis.tw. (91)  
 3 exp Pelvic Pain/ (0)  
 4 (Pelvic adj2 Pain).tw. (248)  
 5 Dyspareunia/ (134)  
 6 Dyschezia\$.tw. (3)  
 7 Dyspareunia\$.tw. (267)  
 8 (pain\$ adj2 bowel movement\$).tw. (6)  
 9 exp Ovariectomy/ (1115)  
 10 Ovariectomy\$.tw. (2403)  
 11 oophorect\$.tw. (108)  
 12 (remov\$ adj2 ovar\$).tw. (40)  
 13 (salpingo adj ovariectomy).tw. (0)  
 14 (surgic\$ adj3 menopause).tw. (64)  
 15 or/1-8 (589)  
 16 or/9-14 (2634)  
 17 15 and 16 (3)  
 18 exp hormone replacement therapy/ or exp estrogen replacement therapy/ (1056)  
 19 (Hormone adj2 therap\$).tw. (971)  
 20 HRT.tw. (361)  
 21 Tibolone.tw. (18)  
 22 exp Estrogens/ (3495)  
 23 exp Progesterone/ (1390)  
 24 (Estrogen\$ or Progest\$).tw. (5595)  
 25 or/18-24 (7349)  
 26 17 and 25 (1)

27 from 26 keep 1 (1)

### Appendix 3. CINAHL

- 1 exp Endometriosis/ (566)
- 2 Endometriosis.tw. (463)
- 3 exp Pelvic Pain/ (775)
- 4 (Pelvic adj2 Pain).tw. (517)
- 5 Dyspareunia/ (150)
- 6 Dyschezia\$.tw. (1)
- 7 Dyspareunia\$.tw. (143)
- 8 (pain\$ adj2 bowel movement\$).tw. (5)
- 9 exp Ovariectomy/ (448)
- 10 Ovariectomy\$.tw. (145)
- 11 oophorect\$.tw. (276)
- 12 (remov\$ adj2 ovar\$).tw. (20)
- 13 (salpingo adj ovariectomy).tw. (0)
- 14 (surgic\$ adj3 menopause).tw. (76)
- 15 or/1-8 (1672)
- 16 or/9-14 (674)
- 17 15 and 16 (35)
- 18 exp hormone replacement therapy/ or exp estrogen replacement therapy/ (4517)
- 19 (Hormone adj2 therap\$).tw. (2363)
- 20 HRT.tw. (1006)
- 21 Tibolone.tw. (57)
- 22 exp Estrogens/ (4247)
- 23 exp Progesterone/ (788)
- 24 (Estrogen\$ or Progest\$).tw. (3460)
- 25 estra\$.tw. (790)
- 26 or/18-25 (9451)
- 27 17 and 26 (10)
- 28 exp clinical trials/ (57427)
- 29 Clinical trial.pt. (29998)
- 30 (clinic\$ adj trial\$1).tw. (13150)
- 31 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. (7801)
- 32 Randomi?ed control\$ trial\$.tw. (11197)
- 33 Random assignment/ (17445)
- 34 Random\$ allocat\$.tw. (1211)
- 35 Placebo\$.tw. (10846)
- 36 Placebos/ (4145)
- 37 Quantitative studies/ (3735)
- 38 Allocat\$ random\$.tw. (73)
- 39 or/28-38 (79254)
- 40 27 and 39 (2)
- 41 from 40 keep 1-2 (2)

## Appendix 4. CENTRAL

- 1 exp Endometriosis/ (347)
- 2 Endometriosis.tw. (581)
- 3 Pelvis Pain Syndrome/ (0)
- 4 (Pelvic adj2 Pain).tw. (309)
- 5 Dyspareunia/ (43)
- 6 Dyspareunia\$.tw. (133)
- 7 Dyschezia\$.tw. (4)
- 8 (pain\$ adj2 bowel movement\$).tw. (13)
- 9 exp ovariectomy/ or exp salpingoophorectomy/ (190)
- 10 Ovariectomy\$.tw. (65)
- 11 salpingoophorectomy\$.tw. (1)
- 12 oophorect\$.tw. (293)
- 13 (remov\$ adj2 ovar\$).tw. (11)
- 14 (salpingo adj ovariectomy).tw. (0)
- 15 (surgic\$ adj3 menopause).tw. (76)
- 16 or/1-8 (954)
- 17 or/9-15 (472)
- 18 16 and 17 (20)
- 19 exp Hormone Substitution/ (0)
- 20 (Hormone adj2 therap\$).tw. (2360)
- 21 (hormone adj3 substitut\$).tw. (53)
- 22 HRT.tw. (1012)
- 23 exp Tibolone/ (0)
- 24 Tibolone.tw. (309)
- 25 exp Estrogen/ (3675)
- 26 exp Progesterone/ (1787)
- 27 tibolone.tw. (309)
- 28 (Estrogen\$ or Progest\$).tw. (5916)
- 29 estra\$.tw. (3383)
- 30 or/19-29 (10176)
- 31 18 and 30 (8)
- 32 from 31 keep 1-8 (8)

## Appendix 5. EMBASE

- 1 exp Endometriosis/ (10166)
- 2 Endometriosis.tw. (8803)
- 3 Pelvis Pain Syndrome/ (4221)
- 4 (Pelvic adj2 Pain).tw. (3474)
- 5 Dyspareunia/ (2069)
- 6 Dyspareunia\$.tw. (1403)
- 7 Dyschezia\$.tw. (79)
- 8 (pain\$ adj2 bowel movement\$).tw. (36)
- 9 exp ovariectomy/ or exp salpingoophorectomy/ (18093)
- 10 Ovariectomy\$.tw. (14109)
- 11 salpingoophorectomy\$.tw. (107)
- 12 oophorect\$.tw. (4363)
- 13 (remov\$ adj2 ovar\$).tw. (576)
- 14 (salpingo adj ovariectomy).tw. (7)
- 15 (surgic\$ adj3 menopause).tw. (481)
- 16 or/1-8 (16927)
- 17 or/9-15 (24421)

18 16 and 17 (830)  
 19 exp Hormone Substitution/ (25640)  
 20 (Hormone adj2 therap\$).tw. (14911)  
 21 (hormone adj3 substitut\$).tw. (640)  
 22 HRT.tw. (6186)  
 23 exp Tibolone/ (1638)  
 24 Tibolone.tw. (754)  
 25 exp Estrogen/ (117030)  
 26 exp Progesterone/ (37148)  
 27 tibolone.tw. (754)  
 28 (Estrogen\$ or Progest\$).tw. (95948)  
 29 estra\$.tw. (44850)  
 30 or/19-29 (183085)  
 31 18 and 30 (280)  
 32 Clinical trial/ (495185)  
 33 Randomized controlled trials/ (155511)  
 34 Random Allocation/ (25203)  
 35 Single-Blind Method/ (7410)  
 36 Double-Blind Method/ (68576)  
 37 Cross-Over Studies/ (20046)  
 38 Placebos/ (111054)  
 39 Randomized controlled trial\$.tw. (28060)  
 40 RCT.tw. (2194)  
 41 Random allocation.tw. (605)  
 42 Randomly allocated.tw. (9592)  
 43 Allocated randomly.tw. (1314)  
 44 (allocated adj2 random).tw. (552)  
 45 Single blind\$.tw. (7066)  
 46 Double blind\$.tw. (81296)  
 47 ((treble or triple) adj blind\$).tw. (127)  
 48 Placebo\$.tw. (104327)  
 49 Prospective Studies/ (73142)  
 50 or/32-49 (651841)  
 51 Case study/ (5369)  
 52 Case report.tw. (110903)  
 53 Abstract report/ or letter/ (461484)  
 54 or/51-53 (575754)  
 55 50 not 54 (629234)  
 56 animal/ (18235)  
 57 human/ (6058876)  
 58 56 not 57 (14465)  
 59 55 not 58 (629138)  
 60 31 and 59 (49)  
 61 from 60 keep 1-49 (49)

## HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 1, 2009

## CONTRIBUTIONS OF AUTHORS

Hanan Al Kadri (HK) and Ali Hajeer (AH) screened titles and abstracts independently. They discarded studies that were not applicable. HK and AH also independently assessed the retrieved abstracts and, when necessary, ordered the full texts of these studies to determine which study satisfied the inclusion criteria.

The same review authors also carried out data extraction independently. They resolved disagreements in consultation with the other two authors, Samar Hassan (SH) and Haya AlFozan (HF).

SH and HF independently assessed the quality of studies to be included. They resolved discrepancies by discussion with HK and AH. HK wrote the final manuscript and together with AH produced the final review.

## DECLARATIONS OF INTEREST

We certify that we have no affiliations or involvement in any organization or entity with a direct financial interest in the subject matter of the review (from, for example, employment, consultancy, stock ownership or honoraria).

## SOURCES OF SUPPORT

### Internal sources

- National Guard Health Affairs, Cochrane Review Group, Saudi Arabia.

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- Cochrane Menstrual Disorders And Subfertility Group, New Zealand.